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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Gentlemen,

I am responding to your request for comments on a draft Guidance document on "Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis." This Guidance draft was generated because of the finding of osteosarcoma in rodents; the FDA suggestions with regard to clinical trials and consent forms are appropriate. However, I do not believe that this problem is a major one associated with parathyroid hormone since osteosarcoma is rare, and only occurs at high doses in the rapidly developing young animals. I have enclosed my summary of the considerations that need to be taken into account with PTH and PTH_{RP} in humans so that a better draft Guidance can be developed. PTH and PTH_{RP} may not have the desired effect on fracture reduction, and could in fact increase fracture. Moreover, these agents could have extremely serious side effects based on recent findings in hyperparathyroidism. My comments are based on 35 years of experience in metabolic bone disease, which includes background in both primary and secondary hyperparathyroidism. I was a member of the FDA committees that established early Guidelines for osteoporosis trials. I also have 35 years of experience in measurements of bone mineral density (BMD) by noninvasive technologies, which enables me to comment on the difficulties of using BMD, whether by DEXA or QCT, as an end-point for studies on PTH and PTH_{RP}.

Please be aware that I am currently President and Chairman of the Board of Lunar Corporation, a leading manufacturer of bone densitometers; however, I will be resigning from that position on August 8 when Lunar Corporation is acquired by General Electric Medical Systems. I am also Chairman of the Board of Bone Care International, a manufacturer of an active vitamin D agent used in treating secondary hyperparathyroidism in dialysis patients. I do not believe that these positions entail a significant conflict of interest with regard to PTH and PTH_{RP} treatment of osteoporosis.

Sincerely yours,

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RBM/lc
Enclosure
cc: Leo Lutwak, M.D. - FDA
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Difficulties With Use of PTH and PTH_{RP} for the Prevention and Treatment of Osteoporosis

1. Mechanism of Action

PTH and PTH_{RP} are stimulators of bone turnover; they affect both osteoblastic formation (in trabecular bone) and osteoclastic resorption (in compact bone) [1-3]. The principal result of increased PTH levels is a thickening of trabecular bone, but with decreased mineralization. Compact bone is adversely influenced; experimental studies over the past 70 years have shown that PTH excess is associated with endocortical erosion, decreased mineralization, and increased porosity [4-7]. In rats, without Haversian remodeling, the potential for decreased strength is much less than in humans [6]. **The mechanism of action and skeletal effects are comparable to high-dose fluoride administration, and in this regard at least PTH and PTH_{RP} could be called "fluoride mimetics."**

2. Skeletal Effects

Studies in both primary and secondary hyperparathyroidism in humans, and animal models, show overall loss of bone. There have been several hundred studies showing this loss. Even the modest elevation of PTH in lactating women is associated with both spine and femoral loss [8]. The episodic administration of exogenous PTH leads to thickening of trabecular bone *in vivo*, but loss of compact bone. This loss has been demonstrated in several studies when PTH is given without a concomitant antiresorptive agent [9-13]. In the latter studies, there was a 5 to 10% increase of spine BMD (by DEXA), but a 2 to 4% decrease of total body BMD, over a one-year period (see Figure below). The latter represents a truly profound loss in total body calcium reserves. This loss of compact bone can be prevented by concomitant administration of an antiresorptive agent such as estrogen or a bisphosphonate [13-18], as is also the case with fluoride [19,21].

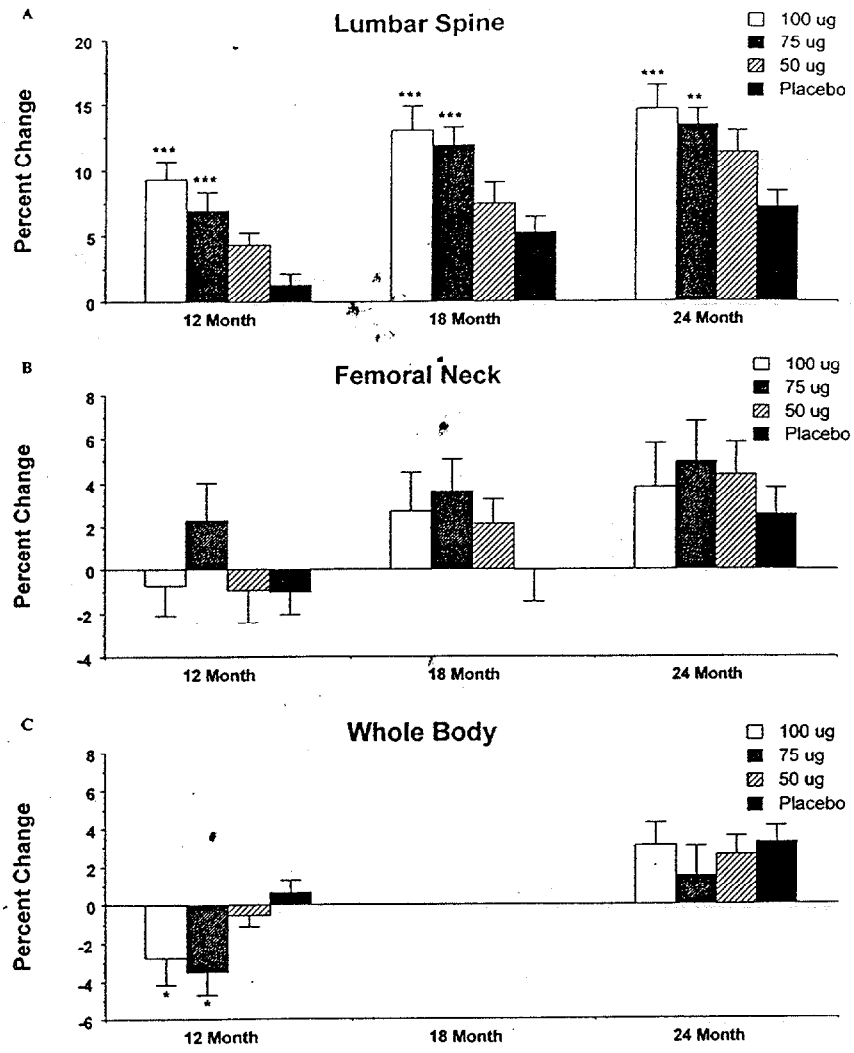

Figure 1. BMD (percent change from baseline; mean ± SEM) in postmenopausal women given 100, 75, or 50 μg PTH or placebo during the first year followed by 10 mg alendronate daily during the second year. Month 12 data represent the changes observed after 1 yr of PTH or placebo. Month 18 and month 24 data represent the changes observed after an additional 6 and 12 months of alendronate treatment, respectively.

*P<0.05; **P<0.01; ***P<0.001 (compared to placebo/alendronate group)

From Rittmaster et al, *J Clin Endocrinol Metab*, 2000;85:2129-2134.

3. Fracture Consequences

The skeletal consequences of the spinal hypertrophy produced by unopposed PTH are unclear but must be presumed to be comparable to those effects of high-dose fluoride, where fracture rates were actually increased. The reasons are likely to be the same.

It should be noted that biochemical markers of bone turnover are increased significantly by PTH/PTH_{RP}. **High turnover, such as that produced by both high-dose fluoride or PTH, appears to be an independent risk factor for fracture according to several studies [22].** Trabecular hypertrophy does not compensate for the endocortical erosion of the thin (0.3 mm) rim of compacted bone about the vertebral body. The fracture consequences of PTH/PTH_{RP} for other areas, such as the proximal femur, are even less clear. High-dose fluoride is known to increase fracture rates of the proximal femur, and this may also occur with PTH. The fact that femur BMD by DEXA increases is no indication of fracture resistance in this case because femur BMD cannot indicate the structural defect caused by cortical porosity or endocortical resorption. Small point defects in the compact bone of the proximal femur have now been pinpointed as the critical factor in strength of fracture resistance [23,24]. Similarly measurements by conventional QCT cannot indicate whether there is loss or preservation of compact bone. One well-known partial-volume artifact, produced by thickened trabeculae and/or increased red marrow, can cause the artificial appearance of increased compact bone with PTH/PTH_{RP} treatment [25]. Even extremely high-resolution QCT, would not allow evaluation of the microscopic effects on the 1 mm thick wall of the proximal femur, the region that is critical to fracture. Several studies have shown an increased rate of fracture, particularly osteoporotic fracture of the ribs, pelvis, and vertebra in patients with mild primary hyperparathyroidism [26-29]. **Consequently the endpoints of trials using PTH and PTH_{RP} as osteoporosis agents must be clinical fracture rather than BMD increase.**

4. Safety Concerns

Extensive studies have been done in patients with primary and secondary hyperparathyroidism that suggest the nature of safety studies that must be done in any clinical trials of PTH and PTH_{RP} even though the doses may be both episodic and low. It must be remembered that the biological effects of episodic dosing is high (since PTH release *in vivo* is episodic); it must not be assumed that the safety effects would be minimal since so long as the trabecular hypertrophy effect is fairly large.

Patients with secondary hyperparathyroidism are known to suffer from: (1) increased fracture rates [26-29], (2) increased heart disease [28-31], (3) increased extraskeletal calcification, (4) psychiatric disorders [29,32], (5) muscular weakness [33,34], and (6) increased risk of cancer [35-40]. Some of these ailments have been ascribed as secondary to renal disease (or the use of calcium salts for binding phosphate). However, these same disorders are evident in patients with mild primary hyperparathyroidism. Of particular concern is the growing evidence that elevated PTH may of and by itself be a cancer promoter [37], much as growth hormone is a cancer promoter. The net effect of mild hyperparathyroidism is an increased death rate [41,42].

All clinical trials involved with PTH should require extensive monitoring for:

(1) extraskeletal calcification
(2) cancer
(3) fractures
(4) psychiatric disorders
(5) muscle weakness
(6) hypertension
(7) heart disease
(8) death rate

Moreover, any Phase IV studies of PTH/PTH_{RP} should be long-term (5 years) and have sufficient power to provide assessments of all of the above-noted potential side effects.

5. Conclusions:

PTH and PTH_{RP} are potent hormonal stimulators of trabecular bone with potential skeletal effects similar to high-dose fluoride. All studies of PTH and PTH_{RP} preferably should be done with a concomitant antiresorptive, or should include at least one arm with a concomitant antiresorptive. Any treatment with unopposed PTH/PTH_{RP} should be limited to one year and followed by antiresorptive therapy. **An important consideration in trials of PTH/PTH_{RP} will be exclusion criteria. Obviously patients with a previous history of long-bone fractures should not be included, and there may be reasons for excluding any patient with any fracture or with femur BMD <-2.5 SD.** In addition, patients with a familial history, or individual history, for any of the noted potential side effects, or with risk factors for those side effects, should be excluded. With regard to endpoints, BMD by DEXA, or trabecular bone density by QCT, are not adequate surrogates for bone strength and fracture resistance with such treatment. BMD can be used as a safety variable for the femur neck and total body rather than spine BMD. Only clinical osteoporotic fracture should be used as an endpoint. Spinal deformation (see enclosed report from the LunarNews on "fake fractures") should not be used as a clinical endpoint because the deformations ascertained by this approach have little relevance to clinical reality. **Finally, extensive safety studies need to be done with regard to Phase III trials, and these safety studies need to be continued into Phase IV.**

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